Psychoactive Drugs as Mental Illness Treatment

Overview

Why use psychoactive drugs to treat mental illnesses?

Examples of effective psychoactive drugs

Evaluation of psychoactive drugs

Ethical Considerations

Future Directions and Conclusions

Interactive Task

Introduction

Why use psychoactive drugs to treat mental illnesses?

Failures of Conservative Treatment

- treatment resistance (30-50% resistance to first-line antidepressants)
- slow onset (e.g SSRIs take 4-8 weeks to start working; CBT requires weeks/months)
- limited utility for crisis situations (e.g. suicidality/self harm)
- delayed mechanism of action
- relapse when treatment stops
- side effects: emotional blunting, weight gain, sexual dysfunction, sleep disturbances
- limited impact on underlying neurobiology
- treatment selection remains trial & error
- barriers to psychotherapy

What about psychoactive drugs?

- rapid effects (hours not weeks)
- effective for treatment-resistant individuals
- targets different brain systems that promote neuroplasticity

Ketamine to treat Depression

Ketamine

- dissociative anesthetic with rapid antidepressant effects
- affects glutamate system by ***blocking NMDA receptors***
  - increases glutamate release
  - enhances synaptic connectivity (esp. PFC)

Major Depressive Disorder

- characterised by ***persistent low mood*** and/or loss of interest/pleasure, along with cognitive and physical symptoms that ***impair daily functioning*** (American Psychiatric Organisation, 2022)

Psychopathology of MDD

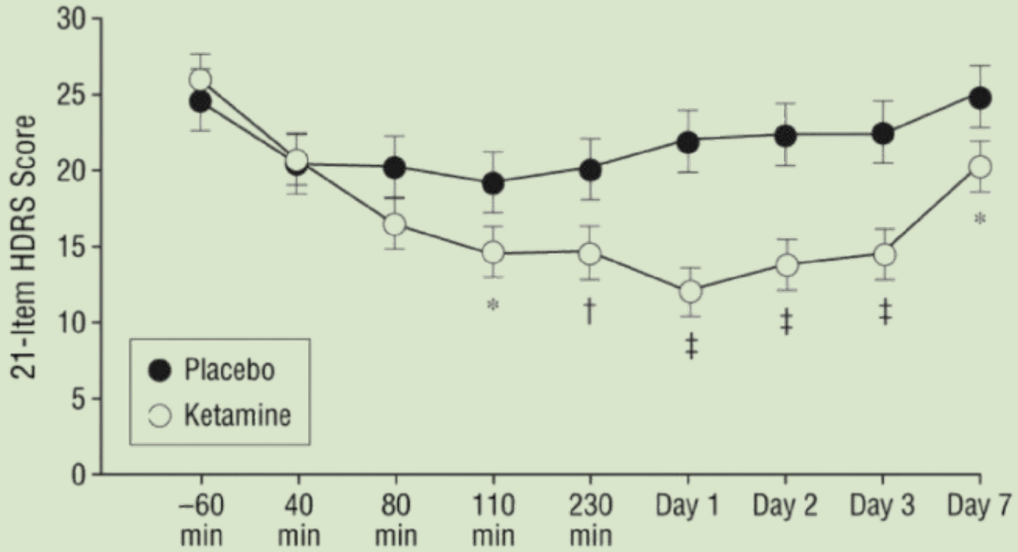
- dysfunction of glutamatergic system, primarily in ***cortico-limbic*** (emotional regulation) & ***corticostriatal*** (reward/motivation) pathways (Zarate et al., 2006)

Rapid-Acting Antidepressants (RAADs): Ketamine

Ketamine vs. placebo in treatment-resistant depression

Study Design

- depression symptoms assessed via ***21-item HDRS***
- intravenous infusions of saline solution & 0.5 mg/kg of ketamine
- 1 week apart, randomized double-blind crossover design
- n = 17 (ketamine), n = 14 (placebo)
- met ***DSM-IV-TR for MDD***



Zarate et al. (2006)

Results

- ketamine group showed sign. improvement in depression within 110 min of injection
- ketamine group improvement remained sign. throughout week
- ***effect size for drug difference:*** large for 24hrs d = 1.46 (95% CI, 0.91-2.01); moderate-large for 7 days d = 0.68 (95% CI, 0.13-1.23).

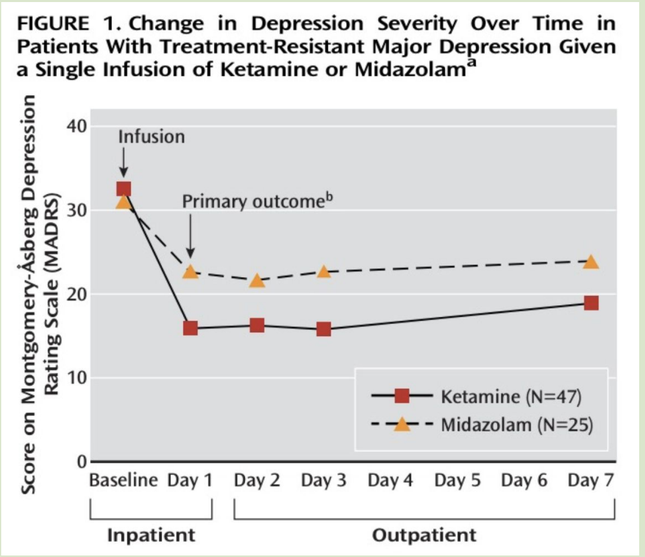
Evaluation

- ***adverse effects of ketamine:*** perceptual disturbances, confusion, euphoria, dizziness etc. *(ceased 80 min after infusion)*
- ***mostly severe depression***
- ***small sample size*** → 3 diff analyses types showed sign. effect
- ***true drug effect:*** time of onset & course of antidepressant effects after 1 dose of ketamine nearly identical for each subject
- ***meta-analysis*** → ketamine vs. other NMDAR antagonists more effective (Kishimoto et al., 2016)

Rapid-Acting Antidepressants (RAADs): Ketamine

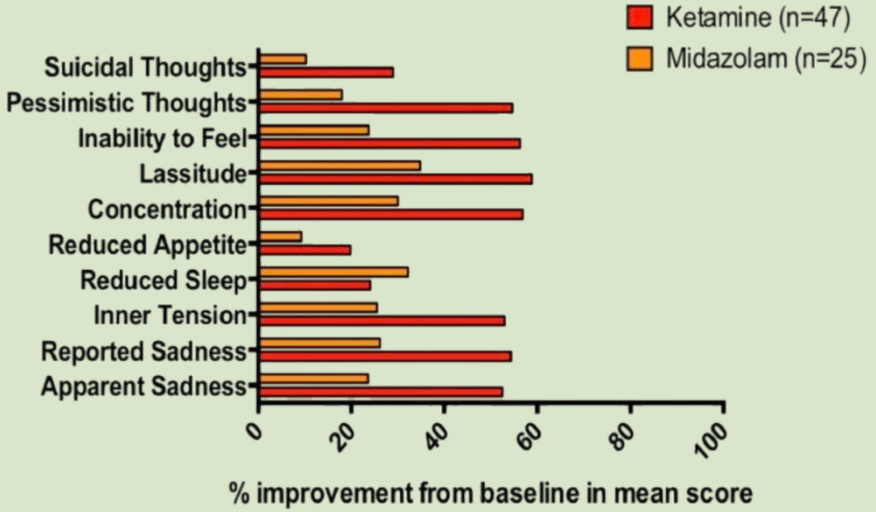
Ketamine vs. midazolam in treatment-resistant depression

- ***midazolam:*** active placebo (fast-acting, short-term sedative used in research)
- ketamine improved depressive symptom severity after 24 hours & sign. more than midazolam



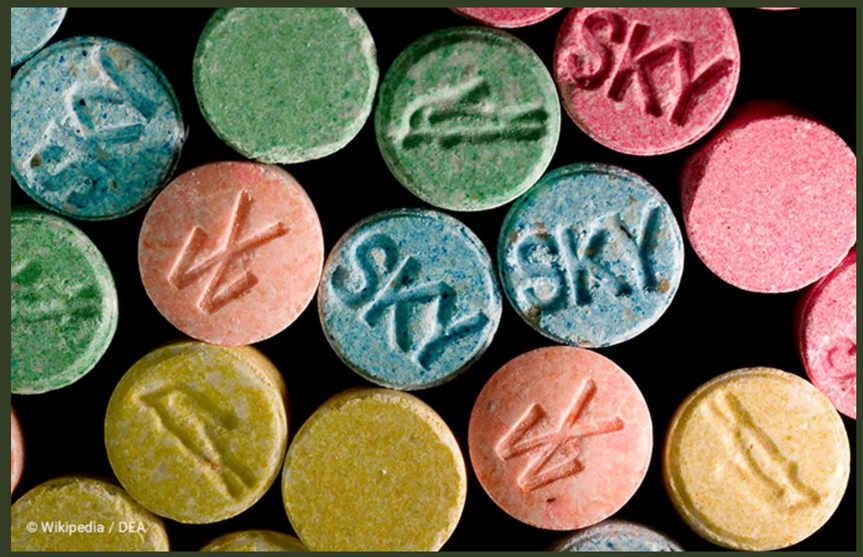
Use of ketamine in depression treatment

- antidepressant effects emerge within hours, peak 24-72 hrs, dissipate within 2 weeks
- single dose effective in ⅓ individuals with failed response to traditional antidepressants
- also effective for bipolar depression (where SSRIs aren't)
- effective in reducing suicidal ideation (Krystal et al., 2013)



Murrough et al. (2013)

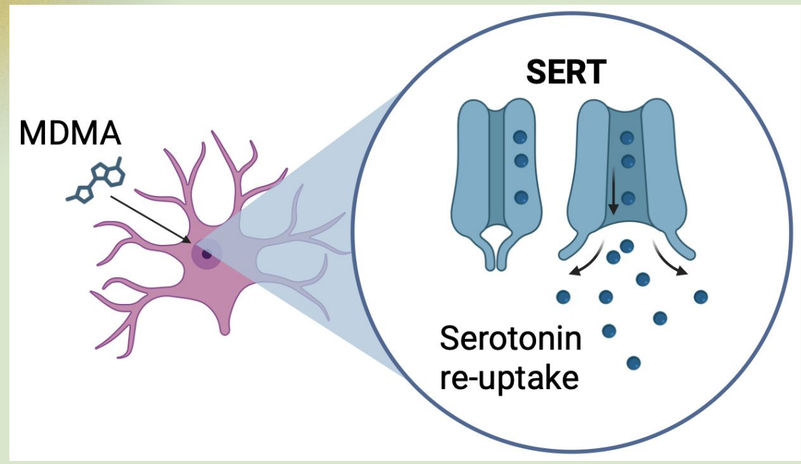
MDMA to treat PTSD



Serotonergic Classical Psychedelics: MDMA

Mechanism of action

- Acts as a **releasing agent for the 5-HT receptor** among others, leading to supra-physiological levels of **serotonin, dopamine, and norepinephrine**
- Stimulates the **release of hormones** including oxytocin, ADH, and cortisol
- **Dampens the amygdala response**



PTSD

"A mental health disorder that occurs as a **result of exposure to traumatic events**, specifically actual or threatened death, serious injury, and/or sexual violence" (5th ed.; DSM–5; American Psychiatric Association, 2013)

Pathophysiology of PTSD

- **Norepinephrine dysregulation**
- **Hyperactive amygdala** (fear center)
- **Hypoactive prefrontal and frontal cortices** (emotional regulation)

MDMA – a treatment option for PTSD?

Serotonergic Classical Psychedelics: MDMA

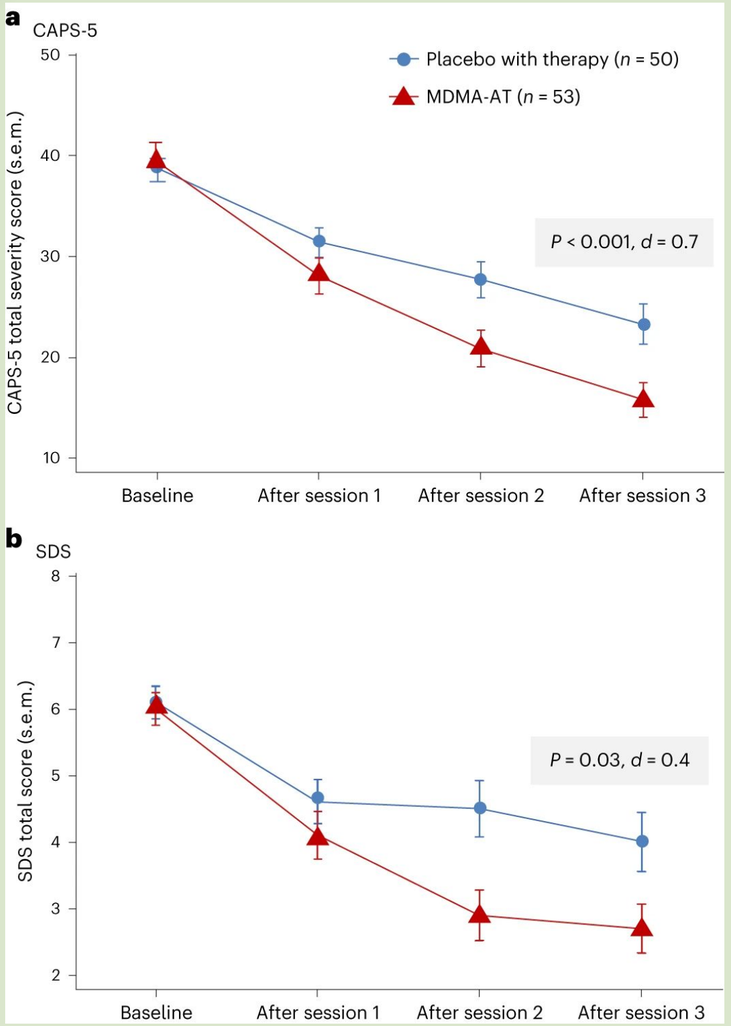
MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial

Study Design:

- Multisite, randomised, double-blind, placebo-controlled phase 3 RCT
- n = 104 adults with moderate-severe DSM-5 PTSD
- 3 x 8-hour sessions **MDMA 80-120 mg or placebo + psychotherapy**
- **CAPS-5 total severity score and Sheehan Disability Scale**

Results:

- **CAPS-5 reduction: -23.7 (MDMA)** vs -14.8 (placebo); p<0.001, d = 0.70
- 71% of MDMA participants no longer met PTSD criteria vs 48% placebo
- **SDS functional impairment significantly improved**
- No serious drug-related adverse events: no MDMA abuse or dependence



Mitchell et al. (2023)

Psilocybin and LSD

Serotonergic Drugs

- Psychedelic Compounds affect Serotonin Organization
- Treatment-resistant depression fMRI studies
- Serotonin Reuptake

Mental Health Effects

- Treatment-Resistant Depression
- End-of-life-anxiety
- Substance Use Disorders
  - Alcoholism
  - Tobacco addiction
- Functional Connectivity

(Mackenzie, 2022)

Psilocybin and LSD

(Girn et al., 2022)

Methods

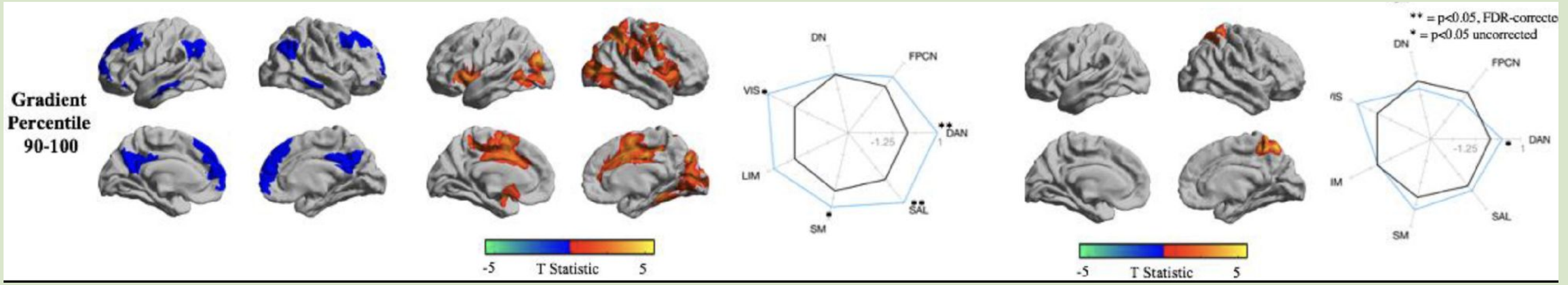
- n = 35, 21+ Healthy participants
- Resting-state BOLD fMRI data
  - 75 µg of LSD & 2 mg of Psilocybin
  - Placebo 10 mL Saline
- Single blind

DAY ONE	DAY TWO	DAY THREE
Resting State Eyes-Closed **No Music**	Resting State Eyes-Closed **With** **Music**	Resting State Eyes-Closed **No Music**

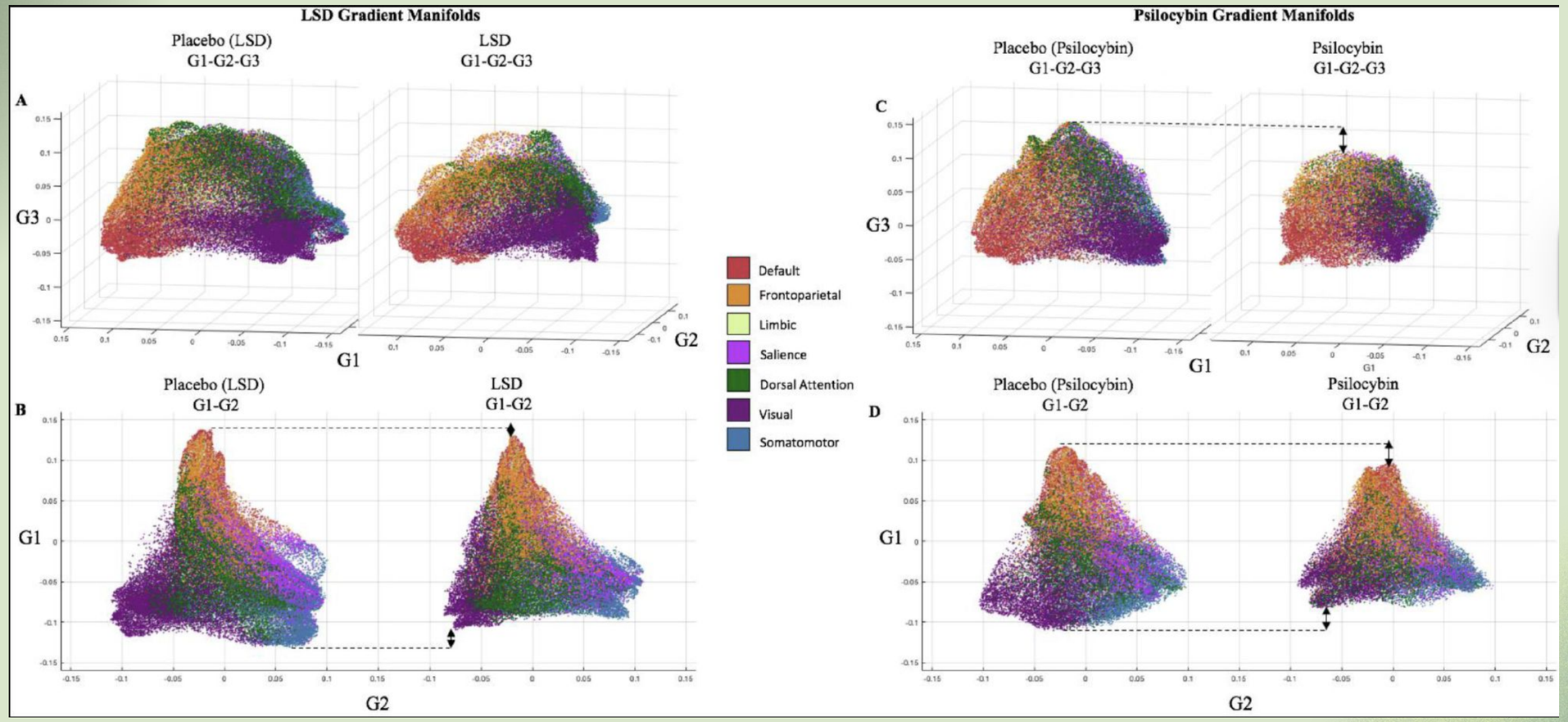
A. Bin-Based ROI

B. LSD > Placebo

C. Psilocybin > Placebo



Results



- Hierarchical Connectivity Flattened under Psilocybin and LSD
- Decision making and sensory systems communicate better
- Depression and Substance Use Disorders highest effect

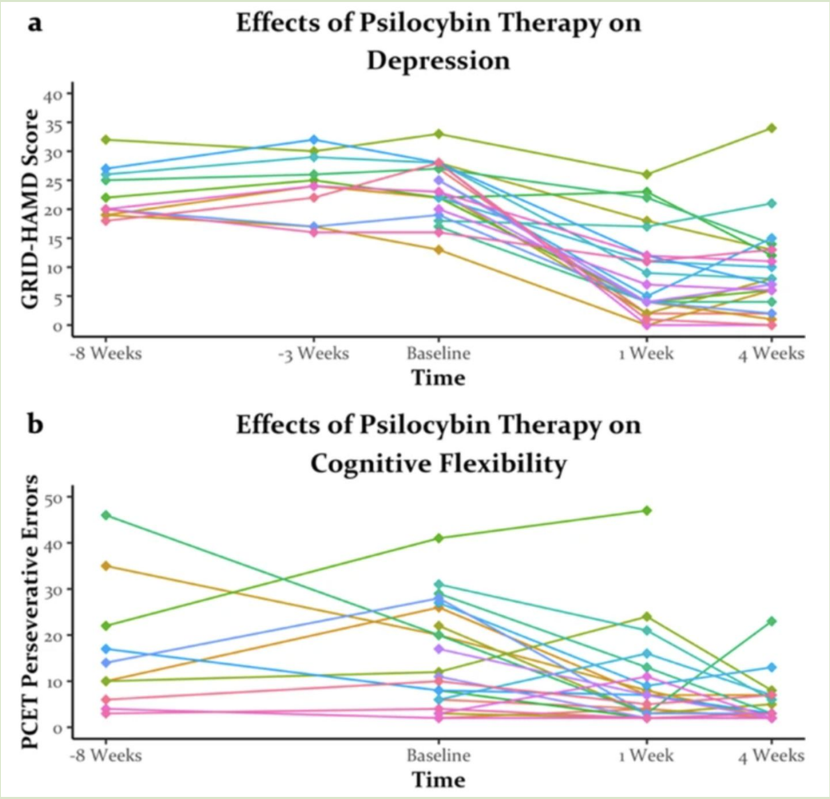
Girn, M., Roseman, L., Bernhardt, B., Smallwood, J., Carhart-Harris, R., & Spreng, R. N. (2022). Serotonergic psychedelic drugs LSD and psilocybin reduce the hierarchical differentiation of unimodal and transmodal cortex. *NeuroImage*, *256*, 119220.

Psilocybin - Depression

Other Methods

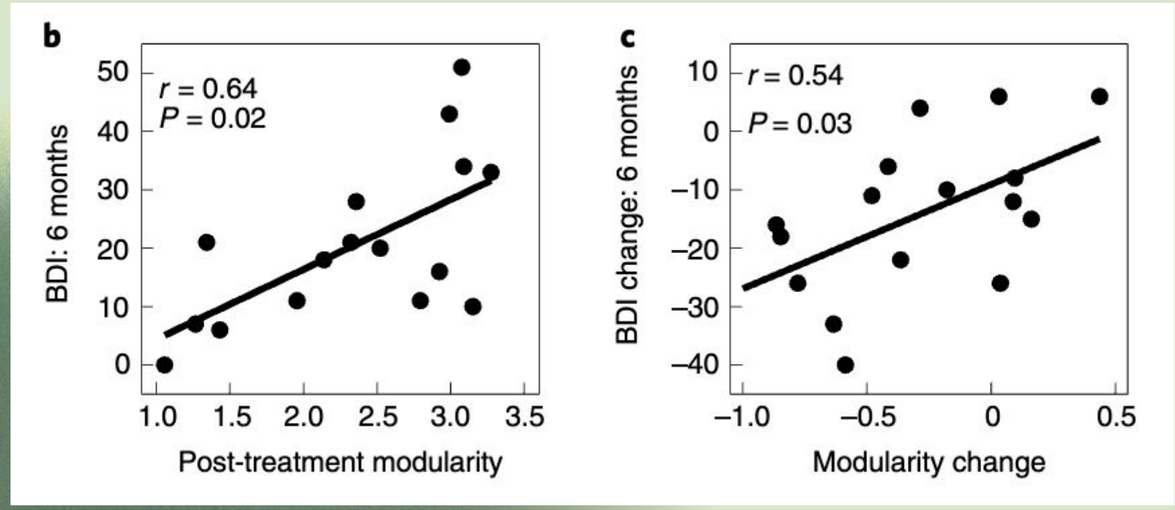
Cognitive Flexibility

- Psilocybin Therapy functionally affects ACC Activity
- Improved treatment for MDD (Doss et al., 2021)



Brain Modularity

- Decreased Brain Modularity (Daws et al., 2022)
  - Increases in Network Integration for TRD



Benefits

Transdiagnostic promise

PTSD, depression, anxiety disorders and many other mental health problems

Efficacy in treatment-resistant populations

Psilocybin in depression and MDMA in PTSD are supported by strong randomised data

Potential for substance use disorders

Ketamine-adjunct therapy in alcohol abuse

Large, consistent effect sizes

A 2024 meta-analysis found psilocybin produced the largest therapeutic effect on mental disorders (g = - 1.49), followed by MDMA (g = -.83) (Yao et al., 2024)

Broad tolerability profile

They tend to be well tolerated across studies, with transient / limited serious drug-related adverse events

Limitations

Main limitations:

- Functional unblinding (Mitchell et al., 2023)
- Low GRADE certainty of evidence (Dominiak et al., 2025; Bahji et al., 2023)
- Small, homogenous samples with inadequate power
- Long-term effects not examined
- Poor side-effect measurement and harm reporting

Other considerations:

- Risk of relapse after discontinuation, dependence & withdrawal (Gianmarco Ingrosso et al., 2024)
- Serotonin toxicity (Malcolm and Thomas, 2021)
- Over-reliance on medication

Ethical Questions

- Informed consent and patient autonomy
- Protection against coercion
- High-risk population for suicidal ideation
- Adverse drug-related events
- Financial incentive for psychotropic research

Carrier et al. (2017), Barber and Dike (2023), Caporuscio et al. (2025)

Future Directions

- Ayahuasca and non-FDA approved Treatments with Cognitive Neuroscientific Backing (Pasquini et al., 2020)
- Longitudinal Studies / Acute Effects
- Overall points:
  - Treatment Resistant Disorders
  - Dissociative Anesthetics - Ketamine
  - Serotonergic - Psilocybin, LSD, DMT, MDMA
  - Combined Talk-Therapy and Drug-based interventions

(Davis, 2015)

Further Readings

Davis, Nick. “The Psychoactive Substances Bill: An Opportunity or Threat for Research? | Nick Davis.” *The Guardian*, 8 June 2015, www.theguardian.com/science/head-quarters/2015/jun/08/the-psychoactive-substances-bill-an-opportunity-or-threat-for-research

Caporuscio, C., Poppe, C., Gieselmann, A., & Dimitris Repantis. (2025). Ethical issues with psychedelic-assisted treatments in psychiatry: A systematic scoping review. *Psychological Medicine*, *55*(e284). https://doi.org/10.1017/s0033291725101761

Reynolds, S. (2023, March 14). *How Psychedelic Drugs May Help with Depression*. National Institutes of Health (NIH). https://www.nih.gov/news-events/nih-research-matters/how-psychedelic-drugs-may-help-depression

References

American Psychiatric Association. (2022). Diagnostic and statistical manual of mental disorders (5th ed., text rev.).

Anees Bahji, Lunsky, I., Gilmar Gutiérrez, & Vázquez, G. (2023). Efficacy and Safety of Four Psychedelic-Assisted Therapies for Adults with Symptoms of Depression, Anxiety, and Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis. *Journal of Psychoactive Drugs*, 57(1), 1–16. https://doi.org/10.1080/02791072.2023.2278586

Barber, G. S., & Dike, C. C. (2023). Ethical and Practical Considerations for the Use of Psychedelics in Psychiatry. *Psychiatric Services*, 74(8). https://doi.org/10.1176/appi.ps.20220525

Caporuscio, C., Poppe, C., Gieselmann, A., & Dimitris Repantis. (2025). Ethical issues with psychedelic-assisted treatments in psychiatry: A systematic scoping review. *Psychological Medicine*, 55(e284). https://doi.org/10.1017/s0033291725101761

Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., … Nutt, D. J. (2017). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific Reports*, 7, 13187. https://doi.org/10.1038/s41598-017-13282-7

Carrier, F., Banayan, D., Boley, R., & Karnik, N. (2017). Ethical challenges in developing drugs for psychiatric disorders. *Progress in Neurobiology*, 152, 58–69. https://doi.org/10.1016/j.pneurobio.2017.03.002

Daws, R. E., Timmermann, C., Giribaldi, B., Sexton, J. D., Wall, M. B., Erritzoe, D., … Carhart-Harris, R. L. (2022). Increased global integration in the brain after psilocybin therapy for depression. *Nature Medicine*, 28(4), 844–851. https://doi.org/10.1038/s41591-022-01744-z

Dominiak, M., Gędek, A., Modrzejewski, S., Permoda-Pachuta, A., & Antosik, A. Z. (2025). Efficacy and Safety of Psychedelics in Mental Disorder Cases: An Umbrella Review of Meta-Analyses of Randomized Controlled Trials. *Journal of Clinical Medicine*, 15(1), 253. https://doi.org/10.3390/jcm15010253

Doss, M. K., Považan, M., Rosenberg, M. D., Sepeda, N. D., Davis, A. K., Finan, P. H., … Barrett, F. S. (2021). Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. *Translational Psychiatry*, 11, 574. https://doi.org/10.1038/s41398-021-01706-y

Gianmarco Ingrosso, Cleare, A. J., & Juruena, M. F. (2024). Is there a risk of addiction to ketamine during the treatment of depression? A systematic review of available literature. *Journal of Psychopharmacology*, 39(1). https://doi.org/10.1177/02698811241303597

Girn, M., Roseman, L., Bernhardt, B., Smallwood, J., Carhart-Harris, R. L., & Spreng, R. N. (2022). Serotonergic psychedelic drugs LSD and psilocybin reduce the hierarchical differentiation of unimodal and transmodal cortex. *NeuroImage*, 256, 119220. https://doi.org/10.1016/j.neuroimage.2022.119220

References

Kishimoto, T., Chawla, J. M., Hagi, K., Zarate, C. A., Jr., Kane, J. M., Bauer, M., & Correll, C. U. (2016). Single-dose infusion ketamine and non-ketamine N-methyl-D-aspartate receptor antagonists for unipolar and bipolar depression: A meta-analysis of efficacy, safety, and time trajectories. *Psychological Medicine*, 46(7), 1459–1472. https://doi.org/10.1017/S0033291716000064

Krystal, J. H., Sanacora, G., & Duman, R. S. (2013). Rapid-acting glutamatergic antidepressants: The path to ketamine and beyond. Biological Psychiatry, 73(12), 1133–1141. https://doi.org/10.1016/j.biopsych.2013.03.026

Mackenzie, R. J. (2022, March 17). An introduction to five psychedelics: Psilocybin, DMT, LSD, MDMA and ketamine. *Technology Networks*. https://www.technologynetworks.com/neuroscience/articles/an-introduction-to-five-psychedelics-psilocybin-dmt-lsd-mdma-and-ketamine-355897

Malcolm, B., & Thomas, K. (2021). Serotonin toxicity of serotonergic psychedelics. *Psychopharmacology*, 239. https://doi.org/10.1007/s00213-021-05876-x

Mitchell, J. M., Ot'alora G. , M., van der Kolk, B., Shannon, S., Bogenschutz, M., Gelfand, Y., Paleos, C., Nicholas, C. R., Quevedo, S., Balliett, B., Hamilton, S., Mithoefer, M., Kleiman, S., Parker-Guilbert, K., Tzarfaty, K., Harrison, C., de Boer, A., Doblin, R., & Yazar-Klosinski, B. (2023). MDMA-assisted Therapy for Moderate to Severe PTSD: a randomized, placebo-controlled Phase 3 Trial. *Nature Medicine,* 29(29), 1–8. https://doi.org/10.1038/s41591-023-02565-4

Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., & Mathew, S. J. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. *American Journal of Psychiatry*, 170(10), 1134–1142. https://doi.org/10.1176/appi.ajp.2013.13030392

Pasquini, L., Palhano-Fontes, F., & Araujo, D. B. (2020). Subacute effects of the psychedelic ayahuasca on the salience and default mode networks. *Journal of Psychopharmacology*, 34(6), 623–635. https://doi.org/10.1177/0269881120909409

Yao, Y., Guo, D., Lu, T.-S., Liu, F.-L., Huang, S.-H., Diao, M.-Q., Li, S.-X., Zhang, X.-J., Kosten, T. R., Shi, J., Bao, Y.-P., Lu, L., & Han, Y. (2024). Efficacy and safety of psychedelics for the treatment of mental disorders: a systematic review and meta-analysis. *Psychiatry Research (Print)*, 335(1), 115886–115886. https://doi.org/10.1016/j.psychres.2024.115886

Zarate, C. A., Jr., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., & Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*, 63(8), 856–864. https://doi.org/10.1001/archpsyc.63.8.856